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13. ABSTRACT *(Maximum 200 Words)*

This report addresses the problem of image registration in cases where pixel-to-pixel correspondence can't be established. Specifically, the interest is in images containing 3-D elastic and nonstructured objects whose appearance varies with acquisition parameters. The work is motivated by the problem of mammogram screening based on comparison between mammograms of the same patient acquired in differenet screenings. Misregistration between temporally spaced screenings arises from minor differences in 3-D positioning and compression, as well as, normal changes in tissue that are function of time. The objective is to identify corresponding regions in two images, similarly to what is done by medical experts. The locations of the regions are determined based on the locations of identifiable landmark points, and each corresponding region's extent is determined by characteristics of the older mammogram. An image pair is covered with overlapping circular regions without gaps and the proposed algorithm provides for further splitting of larger regions. In order to gain an insight into the problem of mammogram misregistration, the work has been extended into problem of mammogram simulation. The developed simulation algorithms encompass the problems of modeling breast tissue, compression and X-ray image acquisition.

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STATEMENT OF THE PROBLEM STUDIED

1. INTRODUCTION

This work is concerned with the problem of detecting early cancerous changes by comparing temporal sequences of mammograms of a same patient. The comparison uses the older mammogram as a reference, and thus the approach may reduce the high rate of false positives associated with many computer-based methods. More importantly, following subtle changes over time may provide for very early cancer detection. However, automating mammogram sequence analysis is a very complex task, and it requires solving a number of subproblems, including standardizing screening procedures, registering mammograms, and characterizing minor changes in texture patterns. The specific goals of the study was to develop and test digital image processing methods that register mammograms (acquired in regular screenings) and provide for regional mammogram comparison with the objective of detecting early cancerous changes. Developed methods are envisioned as an integral part of a computer-based aid for mammogram screening which draws the attention of medical experts to suspicious regions in mammograms. Throughout the course of the study the work was extended into mammogram simulation in order to provide a better insight into understanding features seen in mammograms and effects of changes in acquisition parameters.

The view taken early in this work is that the precise mammogram registration is intractable. This is due to the fact that these images correspond to compressed, elastic 3-D objects and the images differ primarily due to the fact that there are variations in positioning and compression. These variations are in essence changes in viewpoint, and 2-D transformations can not countereffect 3-D changes in viewpoint. This work concentrates on developing an alternative to precise registration by defining corresponding regions in two images, as is done by medical experts. The first step in defining regions is establishing landmarks in a mammogram pair and establishing their correspondence. An important advantage of this approach is that it avoids interpolation inherent in detailed registration and thus provides for meaningful comparison between temporally spaced screenings.

The original focus of the work has been on the problem of establishing correspondence between temporally spaced mammograms of the same patient. More recently the work was extended to the problem of mammogram simulation. This extension was motivated by the desire to get an insight into effects of differences in positioning and compression that give rise to significant differences in appearances of mammogram pairs. Sections 2 and 3 summarize the research in the areas of mammogram registration and simulation, respectively. Details of the work were presented in technical reports to AOR 1997-2000, and in references [1] and [24].

2. PART I: MAMMOGRAM REGISTRATION

Misregistration between temporally spaced screenings arises from minor differences in 3-D positioning and compression, as well as, normal changes in tissue that are a function of time. The objective is to identify corresponding regions in two images, similarly to what is done by medical experts. The locations of the regions are determined based on the locations of identifiable landmark points, and each corresponding regions extent is determined by characteristics of the older mammogram. An image pair is covered with overlapping circular regions without gaps, and the proposed algorithm provides for further splitting of larger regions.

2.1 Technical Approach

From the technical point of view, regional registration of mammograms is the problem of identifying similar regions in weakly structured texture patterns. In the proposed approach a mammogram pair is covered by corresponding circles of varying radii. The circles may overlap but there are no gaps in either image. The locations of the centers of corresponding circles are determined relative to a small set of identifiable points and the radius of each pair is determined by intensity characteristics of the older mammogram.

Detection and correspondence between the identifiable points

In our approach we use intersections of the most prominent elongated structures (milk ducts and blood vessels) as the landmark points. After extracting the intersections in both images, we establish correspondence between the common subset of points. The algorithms used are detailed in the AOR technical reports 1997 and 1998, and in [24].

- *Detection of intersection points.* The intersections are detected by first identifying the elongated structures using the modified monotony operator. The operator is designed to detect roof edges corresponding to the thin elongated structures.

- *Establishing correspondence.* The algorithm is developed assuming that there is similarity between two images. It utilizes two stage processing. First, it forms an accumulator matrix where each entry corresponds to the likelihood that the pair of points (determined by the row and column of the entry) are a match. Next, a measure of similarity employing the geometry of the elongated structures and textural characteristics of the neighborhood is utilized to establish if two points are a likely match.

Establishing regional correspondence

The corresponding regions are selected based on the control points and similarity of texture characteristics. In this research regions are circular. The circular geometry is selected because it is invariant to rotational misalignments arising from image digitization (the images are obtained by digitizing film) and requires determining only the corresponding centers and radii. The essential elements of the procedure involve the following.

- *Determining region centers.* The distances between landmark points are used to determine the centers and the radius for each pair is such that it ensures that the region in the older mammogram belongs predominantly to a single partition. Since the distances between control points are not preserved in two screenings, the region centers are determined as the cluster centers of points obtained by considering all pairwise combinations of matched control points.

- *Determining the extent of corresponding regions.* The radii of the corresponding regions are the same and are determined so that the corresponding regions have similar texture characteristics (this is important for the comparison paradigm). Partitioning of the older mammogram is used to ensure that each region is characterized by predominantly homogeneous texture pattern. Partitioning employs a hierarchical region growing paradigm that uses pyramidal multiresolution image representation.

- *Covering a mammogram pair.* The covering algorithm generates corresponding circular regions and covers an image pair with overlapping circles with no gaps.

2.2 Results

Evaluation of the algorithms was initially carried out using synthetic images designed to independently evaluate the algorithm for the extraction of elongated structures and the correspondence algorithm. The synthetic images were designed to evaluate the algorithms' sensitivity to variations in orientations of elongated structures, their contrast relative to background, background characteristics, noise and parameters employed by the algorithms.
From the experiments detailed in [24], it can be concluded that the algorithms are not sensitive to the mammogram type, changes in the structures' width and are not significantly affected by the type of background. The synthetic mammogram evaluation was used to determine an optimal set of parameters that were used on archived film.

A total of 52 mammogram pairs corresponding to 13 randomly selected cases were available for evaluation. Due to the lack of ground truth regarding control pints, the evaluation was performed by visual inspection. Validation was made independently by three unbiased observers, i.e.., observers who had no knowledge of the algorithm: an experienced radiologist and two untrained observers. A number of experiments was carried out to determine constancy of human performance. The results were analyzed using Komogorov-Smirnov test and the Wilcoxon-Mann-Whitney rank sum test. The study [24] has shown that visual perception of the control points selected by the algorithm is consistent for a single observer. The most important conclusions are that there is an agreement in about 90% of the cases between the algorithm and the medical expert and the algorithms' performance is not affected by the mammogram type.

3. PART II: MAMMOGRAM MODELING AND SIMULATION

The objective of this part of our work is to increase the understanding of relationship between the breast anatomic structures and their appearance in digital mammograms. Our accomplishments up-to-date incorporate rudimental modeling of digital mammograms; the approach comprises of three major steps:

- modeling breast anatomic structures,
- modeling breast tissue compression, and
- modeling X-ray image acquisition.

The breast structures are modeled based on their anatomic properties obtained from description in literature and histologic slice images. Breast compression deformation is estimated using tissue elastic properties and the proposed deformation model. The resulting synthetic mammograms can be used in analysis of positioning and compression effects, and for testing computer algorithms for detection of abnormalities. Developed algorithms are detailed in AOR technical reports 1999 and 2000, and in reference [1].

3.1 Approach

Major tissue types comprising breast anatomy are fibro-glandular tissue (FGT), adipose (fatty) tissue (AT) and pectoral muscles (PM). While the muscular tissue is grouped together and located near the chest wall, the adipose and fibro-glandular tissue are interwoven and distributed throughout the breast volume. Their relative percentage and distribution determine the parenchymal patterns on mammograms and decide whether the breast is classified as ``dense", ``fatty", or ``mixed" type [7].

Radiographically, there are two differing components visible in a mammogram: (i) opaque connective fibrous tissue and ducts and (ii) lucent -- fatty compartments. In addition, one can distinguish microcalcifications and pectoral muscles, which have characteristic intensity, shape,

and location. Ducts are often too small to be resolved by mammography or are obscured by the surrounding connective tissue structures [13]. Visibility of the FGT is affected by the water content and the glandular development related to age. However, the most profound impact on the appearance of the FGT region in a mammogram has the 2D nature of mammographic imaging. Breast 3D structures (ducts and the fibrous elements) are projected onto the 2D film plate in an overlapping manner. Superposition of X-ray attenuation of the overlapped structures produces variety of grey-levels seen in mammograms and also creates characteristic large-scale mammogram texture, called parenchymal patterns. Parenchymal patterns are important since they present the background intensity variations that can corrupt the algorithms for detection of breast abnormalities. In addition, there is no precise definition of the normal breast parenchymal pattern.

<u>Modeling Borders of the AT and FGT Regions</u>

As a first step, our goal was to model 3D breast composition for the purpose of simulating the mammographic medio-lateral (MLO) view. During the MLO view the compression and film plates are positioned tilted for 40-60 degrees from the vertical breast plane toward the axilla. The angle used depends on the orientation of the pectoral muscles, since the compression applied parallel to the PM allows the best visualization of the breast.

The vertical symmetry plane of the proposed 3D breast model corresponds to the MLO view plane. Breast volume is approximated by the quarters of two ellipsoids, attached horizontally at the nipple level, representing the upper and lower breast halves. Dimensions of the ellipsoids are selected from the published data on the average size of the breast subgross histologic slices. Dimensions, (height x width x depth), of the relaxed breast model are:

- 12cm x 10cm x 5cm, upper half -- above the nipple level;
- 5cm x 10cm x 5cm , lower half -- below the nipple level.

The extent of the FGT in our model is bordered by two ellipsoidal surfaces, anterior (front) and posterior (rear), which differ above and below the nipple level. The region between the FGT and the border of the breast volume models the extent of the AT. Dimensions of the FGT region are estimated from the drawings of breast anatomy with inclusion of the axillar FGT extension, Tail of Spence.

<u>Modeling internal structure of the AT and FGT Regions</u>

In our model, internal structure of adipose tissue is represented by the random distribution of the fatty compartments throughout the AT region. Compartments are bounded by thin spherical shells, which are associated with the X-ray and elastic properties of the connective tissue. Compartments themselves -- interiors of the shells -- are associated to the properties of fat. During the random placement of the shells they keep the constant radius until no new compartment can be added without intersecting other spheres. The radius is then decreased and the placement of compartments continues. The thin shells also model the Cooper's ligaments -- attachment of the breast to the subcutaneous skin layer. In the regions near the breast outer border the spheres are allowed to fit only partially within the breast region, so that the intersections of the shells with the breast border model the points where Cooper's ligaments are attached to the skin.

<u>Modeling the FGT Region</u>

The internal structure of the FGT region is modeled using description of the fibro fatty matrix.
The modeling starts by defining a region associated with the X-ray attenuation and elastic properties of the connective tissue, bordered by the anterior and posterior FGT ellipsoids. Fatty cavities are then perforated within the FGT by random placement of the spheres and their interior

is associated with the properties of the adipose tissue. Radii of the cavities are selected in a similar manner as when modeling the AT fatty compartments.

Modeling Ductal Network

Our 3D breast model includes duct network model developed using ramification matrices. This approach is selected because it provides a realistic appearance of duct branching pattern; however, it does not capture underlying breast development process. Ductal network model for our mammography simulation uses ramification matrix corresponding to a random binary tree [15, 19]. This matrix was selected after analysis of small number of available ductograms. Our 3D model of the breast ductal network consists of several ramified trees, each representing a duct lobe. Duct curvature is modeled by modifying a vertical tree, generated using a ramified matrix, to follow an anticipated lobe direction -- a curved path between lobe starting point in the ampulla beneath the nipple and the final point on the posterior edge of the FGT region. The lobe final points were selected assuming that the lobes are placed under approximately equal angles between each other.

Modeling Breast Compression

The model of breast compression described here includes deformation of the large-scale anatomic structures (i.e., the AT and FGT region borders) with independent analysis of 2D slices of the breast model. Deformations of the internal structures of the AT and FGT are modeled by transforming spherical shape of the fatty compartments and cavities into the ellipsoidal ones. The developed model is an approximation of some aspects of breast compression [6, 8, 16 20].

Deformations of the AT and FGT regions are estimated for each slice positioned normally to the compression plates, using a 2-D composite beam model. The estimation incorporates the following steps:

- *Rectangular Approximation of Breast Model Slice* We model breast deformation during the MLO compression. Modeling starts with slicing the 3D breast model normally to the compression plates. Thickness of the slices corresponds to the vertical resolution of the model that can be selected at the beginning of mammography simulation. A slice of the breast model is replaced by its rectangular approximation. The whole slice region and its FGT part are approximated by the rectangles having the same area and the center of gravity, as the corresponding regions of the slice. In order to compute rectangle sides, we need an additional constraint. Thus, we assume that the rectangle side, parallel to the line nipple -- chest wall is equal to dimension of the corresponding slice region in that direction.
- *Slice Deformation Estimation Using 2D Composite Beam Model* Approximation rectangles keep the same elastic parameters as the corresponding slice regions. There is very little reported in literature about the elastic properties of the breast tissue. It is, however, usually assumed that the human soft tissue is incompressible -- its volume does not change with deformation. We also assumed that the elastic properties of the AT and FGT could be approximated by linear Young's elastic moduli. Our compression model uses the relative ratio of the AT and FGT elastic moduli, which was determined using published values of the ultrasound velocity in different tissue types and relation between the velocity and the elastic modulus. Rectangular slice approximation practically has a shape of a composite 2D elastic beam, positioned between two bars corresponding to the compression plates. Breast deformation is estimated by applying the force to the compression plates which in turn deforms the composite beam. As a first approximation our compression model assumes the uniform distribution of the mammographic compression force across the slice. The intensity of the compression force is included indirectly, by assuming the thickness of the compressed breast. Application of the Hooke's law to the rectangular approximation yields the deformed 2D composite beam.

- *Computing Compressed Slice from Deformed Rectangular Approximation* The final step of deformation estimation is computation of the compressed breast slice from its deformed rectangular approximation. In our preliminary work, we have assumed that the breast slice keeps its elliptical shape after the compression. Parameters of the deformed ellipses were computed preserving the region area and dimension along the nipple -- chest wall line. Requirement that the whole FGT region is contained within the borders of the slice was used to define the two elliptical borders of the FGT. The elliptical shape of the compressed breast slice, used in our previous model, does not match the real breast shape. To compensate for the deficiency of our previous approach we have applied correction to the preliminary compression model. Correction assumes that the deformed breast slice consists of (i) a rectangle positioned at the chest wall side and (ii) a semiellipse attached to the rectangle, extending forward to the nipple. Sum of the rectangle and semiellipse area is equal to the whole uncompressed slice area. One side of the rectangle and one axis of the semiellipse are equal to the compressed breast thickness. In order to find the rest of parameters, an additional constraint is needed.

<u>Modeling X-Ray Image Acquisition</u>

Based on the description of X-ray imaging process, relations between the energy imparted during imaging, tissue X-ray attenuation, and the film density (or alternatively, pixel intensity on a digitized image) were derived in the literature [9, 21]. We use these relations in our mammography simulation in order to bridge proposed model of compressed breast anatomic structures and resulting synthetic mammogram.

Mammogram formation is based on the overlapping projection of the breast anatomic structures on a film plate. This overlapped projection of the breast fibro-glandular structures generates characteristic mammographic large-scale texture called parenchymal pattern. Parenchymal patterns are important because they can affect performance of computer methods for detection of abnormalities. By modeling breast anatomic structures and X-ray acquisition process, we have basically simulated large-scale mammogram texture.

The final result of the mammography simulation is a synthetic mammogram. It combines the effects of all three major steps of simulation -- modeling anatomy, compression, and X-ray image acquisition.

3.2 Model Validation

We evaluated our approach to synthetic mammogram generation by comparing the texture of clinical and synthetic mammograms. Assuming that the mammogram texture reflects the 3-D tissue distribution, we hypothesized that the properties of synthetic and clinical texture have similar distribution. Mammogram texture was synthesized by projections of simulated adipose tissue compartments. Size of projected compartments was computed by mathematical morphology. We also computed texture energy and fractal dimension and analyzed the distribution of texture features within four different tissue regions in clinical and synthetic mammograms.

Comparison of the cumulative distributions of the mean features computed from 95 mammograms showed that the synthetic images simulate the mean features of the texture of clinical mammograms. Correlation of clinical and synthetic texture feature histograms, averaged over all subimages, showed that the synthetic images can simulate the range of features seen over a large group of mammograms. The best agreement with clinical texture was achieved for the simulated compartments with radii of 4-13.1 mm in the AT region, and radii of 2.7-5.33mm and 1.3-2.7mm in the retroareolar and dense FGT regions, respectively. The experiments, materials and methods, are detailed in [1].

4. SUMMARY AND CONCLUSIONS

During the first two years of the project, we have developed algorithms for putting mammogram pairs into correspondence, as planned by our original workstatement. This work resulted in the development of novel approaches to determining control points in non-structured texture patterns and establishing correspondence between the sets of determined points in a pair of images. The method for establishing correspondence assigns likelihood to each established correspondence. The performance of the developed methods was first extensively evaluated on synthetic images. This evaluation led to determining optimal parameters that were later used when performing evaluation on real mammograms. Since no ground truth was available for real images, experiments were performed using observers. The first part of experiments concentrated on establishing consistency of human performance, and the second part performed comparison between the performance of human subjects and the developed methods. An agreement of 90% was shown between the performance of our methods and an experienced radiologist.

In the last two years, the project was redirected towards obtaining an insight into effects that positioning and compression have on the appearance of mammograms. Specifically, we have developed simulation algorithms for modeling breast tissue, compression effects and acquisition of X-ray images. The models were validated by comparing complexity of obtained texture patterns with those in real mammograms. The conclusion of the validation study was that there is significant agreement between the two. Consequently, developed simulation methods can be used for validation of various image processing algorithms. Furthermore, these methods can be used in generating test images for our registration methods; specifically, these images would simulate effects of minor changes in acquisition parameters (e.g., compression and positioning) likely to be encountered in clinical practice.

SUMMARY OF THE MOST IMPORTANT RESULTS

In the first phase of the work the following algorithms are the most important developments

- Algorithm for identification of control points in non-structured texture images
- Algorithm for establishing correspondence between landmark points in two mammograms
- Algorithm for establishing regional correspondence between weakly structured texture images
- Development of procedures for evaluation of the algorithms and consistency in human perception of weakly textured patterns

In the second phase, the concentration was on obtaining an insight into problem of establishing mammogram correspondence through mammogram simulation. The primary accomplishments include:

- Modeling of breast tissue characteristics
- Modeling of compression effects
- Modeling of X-ray image acquisition and formation of synthetic mammograms
- Model validation using texture measures to establish similarity between synthetic mammograms and real images.

It is pointed out that the second phase of our work goes beyond the original workstatement, and is in response to a need to develop more reliable algorithms for putting a mammogram sequence into correspondence.

LISTING OF PUBLICATIONS

• Papers published in peer reviewed journals

N. Vujovic and D. Brzakovic: ``Evaluation of an Algorithm for Finding a Match of Distorted Texture Pattern in a Large Image Database," *ACM Transactions on Information Systems*, vol. 16, no. 1, 1998.

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• Papers submitted to journals

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P. Bakic, M. Albert, A. Maidment, and D. Brzakovic: `` Mammogram Synthesis using a 3-D Simulation. II: Evaluation of Synthetic Mammogram Texture``, submitted, Medical Physics, 2002.

• Papers published in conference proceedings

P. Bakic, M. Albert, D. Brzakovic, and A.D.A. Maidment: ``Generation and Evaluation of Physically Inspired Synthetic Mammograms," Proc. World Congress on Medical Physics and Biomedical Engineering, Chicago, IL, July 2000.

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D. Brzakovic, Technical Report to ARO, 1997

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